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38. (Amended) The method of claim 22 wherein the solvent in step (c) is selected from the group consisting of benzene, toluene, benzonitrile, *o*-, ~~—~~ [or] and *p*-xylene, mesitylene, [or] and diphenyl ether; the activated phosphite compound is selected from the group consisting of a mononucleotide phosphoramidite, a dinucleotide phosphoramidite, [or] and a polynucleotide phosphoramidite; the [protetcing] protecting group of the 5'-O-protected nucleoside and the 5'-protected activated phosphite compound is dimethoxytrityl; the phosphorus linked oligomer is selected from the group consisting of a phosphodiester, phosphorothioate [or] and a phosphorodithioate oligonucleotide; and the protic acid is dichloroacetic acid.

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41. (Amended) The method of claim 1 wherein the 5'-protected activated phosphorus compound is a 5'-protected activated H-phosphonate compound; and the phosphorus-linked oligomer is [a] an H-phosphonate oligonucleotide.

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REMARKS

Claims 1 - 41 are pending in this patent application.

The specification has been amended to correct several misspellings and other obvious clerical and grammatical errors, such as pairing of parentheses, capitalization of tradenames, and proper hyphenation.

The Office Action has rejected claims 1-41 under 35 U.S.C. § 112, second paragraph, asserting that the listing of alternative moieties in claims 1, 6, 7, 11, 13,

14, 16, 17, 20, 21, 23-25, 29-31, 33, 34, 37, and 38 is improper because it does not conform to proper Markush terminology. Applicants respectfully point out, however, that Markush terminology is not required in every case of claiming in the alternative. In this regard, MPEP § 2173.01 states that:

> Applicant may use ... alternative expressions ... or any style of expression ... which makes clear the boundaries of the subject matter for which protection is sought.

Further, MPEP § 2173.05(h) states that Markush groups are merely "[o]ne acceptable form of alternative expression." Therefore, where, to the best of Applicant's judgment and belief, the boundaries of the invention are clear in their original form, the existing alternative expressions have not been amended. In response to the rejection, however, many claims have been amended to include Markush terminology where, in Applicants' belief, such language is appropriate. Applicants note that none of the amendments adding Markush terminology to the claims were made in response to any rejection under 35 U.S.C. § 102 or § 103.

Claims 2 and 22 are also rejected under 35 U.S.C. § 112, second paragraph, on the basis that the claims are allegedly indefinite because "the proper placement of the added step within the sequence of steps of the previous [independent] claim has not been specified." However, according to M.P.E.P. § 2173.02,

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary skill in the pertinent art at the time the invention was made.

In this regard, Applicants respectfully refer to the discussion in the specification on page 11 line 35 through page 12 line 11, which states that:

> It is generally preferable to perform a capping step after reaction of the deprotected 5'-hydroxyl with an 5'-protected activated phosphorus compound. The capping step can be performed either before or after the oxidation or sulfurzation step, and is generally known to provide benefits in the prevention of shortened oligomer chains, by blocking chains that have not reacted in the coupling cycle.

Indeed, the specification further incorporates by reference teachings of capping reactions and reagents at, for example, page 29 at lines 11-14. Thus, those of skill in the art, reading the specification, would readily understand the proper placement of the capping step. Accordingly, Applicants respectfully requested that this rejection under § 112, second paragraph, be withdrawn upon reconsideration.

Applicants have amended the claims to correct the obvious typographical errors and misspelled words noted by the Office Action at pages 2 to 3. Applicants also have

amended claims 13 and 30 to provide chemical names for the acronyms DATE and TBTr.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Claims 1-41 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,705,621 to Ravikumar ("Ravikumar") in view of U.S. Patent No. 4,973, 679 to Caruthers et al. ("Caruthers") and further in view of U.S. Patent No. 5,548,076 to Froehler et al. ("Froehler"). The Office Action asserts that Ravikumar teaches "entirely conventional" oligonucleotide synthesis with acetonitrile solvent and an unconventional protecting group, and that Caruthers teaches the use of "any solvent that will dissolve the reactants" including a specific list of organic solvents for phosphoramidite-based-oligonucleotide synthesis. The Office Action further states that Froehler teaches the use of H-phosphonate intermediates for the synthesis of oligonucleotides and phosphorothioate analogs, including "...an anhydrous organic solvent, preferably pyridine/acetonitrile..." The Office Action admits that Applicants' claimed solvents and mixtures thereof are not disclosed in the cited art, but nevertheless asserts that they are obvious because the Caruthers and Froehler references "motivate the selection of practically any organic solvent that will dissolve the reactants." Office Action at page 4. Applicants respectfully assert, however, that the present claims are not obvious, because the cited art, alone or in combination, does not disclose or

suggest the selection of Applicants specific claimed solvents and mixtures, and does not motivate the art skilled to use the same with a reasonable expectation of success.

As will be recognized, claims cannot be found obvious in view of prior art references unless the references themselves suggest that their respective teachings should be modified in a way that would produce the claimed invention. *Berghauser v. Dann*, 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make any necessary modifications. *In re Stencel*, 4 U.S.P.Q.2d 1071, 1073 (Fed. Cir. 1987), *accord*, *Ex parte Marinaccio*, 10 U.S.P.Q.2d 1719 (Pat. Off. Bd. App. 1989). In this respect, the following statement by the Patent Office Board of Appeals is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." .....Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would ***impel*** one skilled in the art to do what the patent applicant has done. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993) (citations omitted; emphasis added).

Significantly, the Office Action identifies no "motivating force" that would have "impelled" persons of ordinary skill to modify the teachings of the cited art to arrive at Applicants' claimed invention.

Applicants have discovered that the deprotection of oligonucleotide synthons can be successfully performed using solvents other than the halogenated alkyl solvents (such as dichloromethane and dichloroethane) that are currently used in solid phase oligonucleotide synthesis, with yields that are comparable to those of existing solid phase oligonucleotide synthesis protocols, thus providing environmental and safety benefits, as well as economic benefits. There is nothing in the art cited by the Office Action that would suggest to the skilled artisan that the customary deprotection protocols used in oligonucleotide synthesis should be modified to employ Applicants' claimed solvents and mixtures. Significantly, there also is no disclosure or suggestion in the cited art that such modification would result in a synthetic protocol having adequate yield of oligomeric product. It is well known in the art of oligonucleotide synthesis that the efficiencies of the individual nucleotide couplings must be extremely high to provide a useful product. Applicants provide herewith a copy of chapter one from Oligonucleotide Synthesis, a Practical Approach, Gait, M.J., Ed. IRL Press, 1996 ("the Gait reference"). Table 2 on page 17 provides theoretical overall yields as a function of the number of nucleotide couplings for oligonucleotides. It can be seen, for example, that for a 20-mer, where the yield of each individual coupling step is 99%, the overall yield of 20-mer oligonucleotide is 81.8%. However, the table shows that even a

small decrease in yield of the individual couplings to 95% results in a drastic reduction in the overall yield to 35.8%. A further decrease in yield of the individual couplings to 90% results in an overall yield of only 12.2%, and a further decrease in yield of the individual couplings to 80% results in an overall yield of only 1.2% Such low overall yields would not be practical for commercial synthesis of oligonucleotides. It is therefore apparent that maintenance of very high efficiency (i.e., yield) is critical to successful oligonucleotide syntheses.

The Gait reference points out the criticality of even small details in established oligonucleotide synthetic protocols, stating on page 18 that:

> It should be recognized that a chemical synthesis method is distinctly different from a biochemical protocol and that a very slight change to a material or method can often make the difference between barely obtaining a usable product and ensuring routinely reliable synthesis.

Further, the Gait reference further points out the criticality of solvent, particularly with respect to the purity, stating in paragraph 5.1 that:

> The synthesizer must ... ensure the highest purity of batches of reagent and solvent... In the author's experience the majority of synthesis failures are caused by impurities in reagents and solvents.

The Gait reference further states at pages 18-19 that:

> Batch to batch variations in solvent quality are a major source of problems, and therefore redisillation of all solvents is recommended.

> the impurities of most concern are water, acids and bases, and metal ions.

Thus, the Gait reference points out criticality of solvent in oligonucleotide synthesis. Given the Gait reference's disclosure of the sensitivity of oligomer yield to solvent composition, the art skilled would not be motivated to change the solvents customarily used in established protocols for solid phase oligonucleotide synthesis.

Because the cited art does not disclose Applicants' claimed invention, and does not provide motivation to use the same with a reasonable expectation of achieving the high yields of customary protocols, Applicants' claimed invention is not obvious over the cited art. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

The applicants believe that the foregoing is completely responsive and that all objections and rejections have been overcome, or else should be withdrawn upon reconsideration. In view of the foregoing, Applicants submit that the claims presently before the Examiner patentably define the invention over the applied art and are otherwise in condition for ready allowance. An early Office Action to that effect is, therefore,

earnestly solicited.

Respectfully submitted,

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